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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/012,846	01/23/98	CHARETTE M	CRF-141

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1647	19

DATE MAILED: 08/21/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/012,846	Charette
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- The MAILING DATE of this communication appears on the cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 6-6-01

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 28-45 is/are pending in the applica

4a) Of the above, claim(s) 28, 33-38 and 43-45 to the extent nonelected is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 28-32 and 37-42 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims 28-45 are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Response to Amendment

1. Claims 28-45 are pending.

Election/Restriction

2. Applicant's election without traverse of Claims 28-45 to the extent of human OP-1 (SEQ ID NO:2) in Paper No. 18 is acknowledged. Applicants migration of the claims to a method of treating damaged hippocampal tissue wherein the morphogen induces dendritic outgrowth of a hippocampal neuron and a method of restoring function is noted, such subject matter differing from previous prosecution. The migration is deemed allowable by the examiner in the interest of furthering prosecution. However, it is noted that a return to the previously claimed subject matter will be considered prosecution of nonelected subject matter.

3. Claims 28, 33-36, 37, 38 and 43-45 drawn to the extent of BMP-2, BMP-5, BMP-6 and 60A are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 18. However it is presently noted that the group is an improper Markusch as there is no common core structure of the previously noted species and thus the species are in fact distinct Groups. At present there is no indication of an allowable generic claim.

Claim Objections

4. Claims 28 and 37-38 are objected to as reciting an improper Markush Group. M.P.E.P. 803.02 states that:

"Since the decisions in In re Weber **,198 USPQ 328 (CCPA 1978); and In re Haas, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention, In re Harnish , 631 F.2d 716, 206 USPQ 300 (CCPA 1980); Ex Parte Hozumi , 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility."

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 28 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 2 which corresponds to the full length mature OP-1 of undisclosed species (at least mouse and human are known). This SEQ ID NO meets the written description provisions of 35 USC 112, first paragraph. However, the claims are directed to or encompass the generic recitation of all representative OP-1, BMP-2, BMP-5, BMP-6 and 60A proteins corresponding to sequences from alternative species, mutated sequences, allelic and splice variants, which sequences differ in identity from the disclosed peptides as set forth in the

specification. Thus, none of these sequences meets the written description provision of 35 USC 112, first paragraph because the specification fails to describe any alternative species, mutated, allelic or splice variants of OP-1, BMP-2, BMP-5, BMP-6 and 60A other than those described as set forth above.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:2 of the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed amino acids and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific amino acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO: 2 of the instant application, but not the full breadth of claims meet the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

7. Claims 28-32 and 37-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for accelerated dendritic outgrowth of hippocampal neurons in culture in the presence of OP-1 as disclosed at p. 61, lines 1-7, does not reasonably provide enablement for the invention as generically claimed for the morphogens recited for inducing dendritic outgrowth as the specification discloses that hippocampal neurons in culture normally exhibit dendritic outgrowth, for restoring function of damaged hippocampal tissue or for stimulating synapse formation. In particular, it is the finding that OP-1 accelerates dendritic outgrowth in culture which is disclosed by applicants specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. In particular, the specification appears to be non-enabling for accelerated dendritic outgrowth of the generically recited morphogens claimed, i.e., multiple species of OP-1, BMP-2, BMP-5, BMP-6 and 60A proteins.

Page 61, lines 1-7 that cultured hippocampal neurons exhibit accelerated dendritic outgrowth in vitro, i.e., at 3 days in comparison to the normal 7-14 days in vitro. However, the

specification fails to teach that OP-1 induces dendritic outgrowth in alternative neurons which are not presupposed to undergo such dendritic outgrowth.

Applicants claims are not limited to dendritic outgrowth in vitro although dendritic outgrowth of hippocampal cells by OP-1 is not tested in vivo. However, at the time of the invention the skilled artisan would have reason to doubt the predictability and effectiveness of OP-1 treatment in vivo for the purpose of accelerating or inducing dendritic outgrowth. In particular, Jackowski et al., Br. J. Of Neurosurgery, 9:303-317, 1995 (previously of record) teaches multiple barriers to the regeneration of neurons in the CNS such as the state of myelination, active inhibitory factors, a lack of neurotrophic support and an intrinsic inability of CNS neurons to regenerate. Thus, in view of the teachings of Jackowski et al., one of skill in the art would have reason to doubt the unsubstantiated assertion that OP-1 is effective to induce dendritic outgrowth of hippocampal neurons in vivo.

In addition, it is noted that the claims recite treating damaged hippocampal tissue and restoring function of damaged hippocampal tissue wherein the morphogen stimulates synapse formation. Although the specification teaches that the OP-1 treated cultures exhibit increased numbers of synapses, such does not provide a nexus from artificial hippocampal cultures to the in vivo situation where the number and proximity of neuronal cells may be limited. In addition, the examiner notes that the cultures exemplified are presumed to be healthy and undamaged and that thus there is no evidence or exemplification to support OP-1's ability to restore damaged hippocampal cells. Indeed, as Jackowski notes CNS neurons may be incapable of rescue upon

injury. Thus, as OP-1 has not been shown to be effective for restoring damaged cells upon injury or for the ability of restoring or maintaining synapses in damaged cells as previously noted, see in particular as previously argued in Paper No. 5, 9-2-99, Varley et al., Wilson et al., Withers et al., and Lein et al., the specification is not commensurate with claims drawn to the treatment of damaged hippocampal tissue, the restoration of function or synapse formation.

In addition, the specifications teachings fails to exemplify dendritic outgrowth potential with molecules other than the full length mature OP-1 as represented by SEQ ID NO:2. In particular it is noted that the specification fails to teach a common core structure of amino acids which is sufficient to provide for dendritic growth of hippocampal neurons either in vitro or in vivo. Applicant's specification appears to conclude that a conserved arrangement of amino acids for the recited molecules is sufficient to provide for dendritic outgrowth in hippocampal neuronal cells. Yet the specification fails to provide for any functional activity based on the conserved amino acid sequences or for the alternative morphogens recited. Further, the specification fails to teach dendritic outgrowth from any other BMP molecule other than that of OP-1 as represented by SEQ ID NO:2. Thus, the skilled artisan would have reason to doubt such molecules utility for the purposes of dendritic outgrowth based on the contradictory disclosures known in the art prior to the invention, in particular Wozney et al., Science 242:1528-34, 1988 teach the utility of the BMP molecules not for dendritic outgrowth potential but for the molecules growth effects in bone and isolation from chondrogenic bone tissue, thus the family name of bone morphogenetic proteins. The skilled artisan at the time of invention and even today readily

recognizes the unpredictable nature in the prediction of protein function based upon divergent, and even conserved structure, see in particular Zheng et al., Pathology, Research and Practice 1992 Dec., 188(8):1104-21 as it relates specifically to BMPs and Skolnick et al., Trends in Biotech., 18(1):34-39, 2000.

Thus, for the aforementioned reasons the skilled artisan would have reason to doubt that the singular in vitro exemplification of accelerated hippocampal dendrite outgrowth in vitro by OP-1, is predictive of inducing hippocampal dendritic outgrowth in vivo as encompassed by the claims.

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation to make and use the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 28-32 and 37-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Reuger et al., WO9403200, 17 February 1994.

Reuger et al., teach morphogen-induced nerve regeneration and repair of damaged neurons and neuronal pathways, see in particular abstract. The subject morphogen includes human and mouse species of OP-1, disclosed as SEQ ID Nos:5 and 6 which share identity with instant SEQ ID NO:2. Reuger et al., teaches OP-1 enhancement of neuronal cell survival, see in particular Example 3, p. 79-81, redifferentiation which includes neuronal cell outgrowth, see in particular Figure 1B, protection from chemical trauma, see in particular Example 5, p. 84-85, nerve-gap repair, see in particular p. 90-93, alleviation of immune response-mediated damage, Example 10, p. 97-99 and repair of neural pathways, see in particular claims 32-33. As the reference teachings of Reuger comprise repairing damaged neurons with OP-1 wherein the treatment comprises contacting neural cells with OP-1 and repairing damaged cells and pathways, the reference teachings and treatment inherently provide for dendritic outgrowth and synapse formation of the claimed hippocampal neurons. Thus, the teachings anticipate the claimed invention.

10. Claims 28-32 and 37-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al., WO9505846, 2 March 1995.

Wang et al., teach neural regeneration, growth and repair of damaged neural tissue using the morphogen BMP-7 which is identical to OP-1 as referenced in US 5,141,905, see in particular abstract. The method of treatment comprises contacting the neural cells with the BMP-7(OP-1) for example as claimed in claim 13-14 and 21 and provides treatment of damaged neural tissue. Thus, the reference teachings are a method which inherently provides dendritic outgrowth

and synapse formation in hippocampal cells as is instantly claimed. Thus, the reference teachings anticipate the claimed invention.

Status of Claims

11. No claims are allowed.

Conclusion

12. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
August 17, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud